11.0 BREAST CANCER

STATEMENT TO THE PUBLIC

The reviewers used two distinct sets of guidelines to evaluate the evidence:

A) Female Breast Cancer

- *Using the traditional guidelines of the International Agency for Research on Cancer (IARC) the DHS Reviewers considered the evidence "Inadequate" (Group 3) to implicate EMFs. This was also the opinion of review panels at IARC and the National Institutes of Environmental Health Sciences (NIEHS).*
- *Using the guidelines developed by the California EMF program one reviewer was "Close to the Dividing Line between Believing and not Believing" and two were "Prone Not to Believe" that EMFs increase the risk of female breast cancer to any degree.*

B) Male Breast Cancer

- *Using the traditional guidelines of IARC the DHS Reviewers considered the evidence "Inadequate" (Group 3) to reach a conclusion. This was also the opinion of review panels at IARC and NIEHS.*

Using guidelines developed by the California EMF program one reviewer was "Close to the Dividing Line between Believing and not Believing" and two reviewers were "Prone Not to Believe" that EMFs increased the risk of male breast cancer to any degree.

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFs) INCREASE DISEASE RISK TO SOME DEGREE
Breast Cancer, Female				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	
	2	3	Prone not to believe	
	3	3	Prone not to believe	
Breast Cancer, Male				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing Line	
	2	3	Prone not to believe	
	3	3	Prone not to believe	

11.1 THE PATTERN OF EPIDEMIOLOGICAL EVIDENCE

Figure 11.1.1 (Female Residential and Electrical Devices)

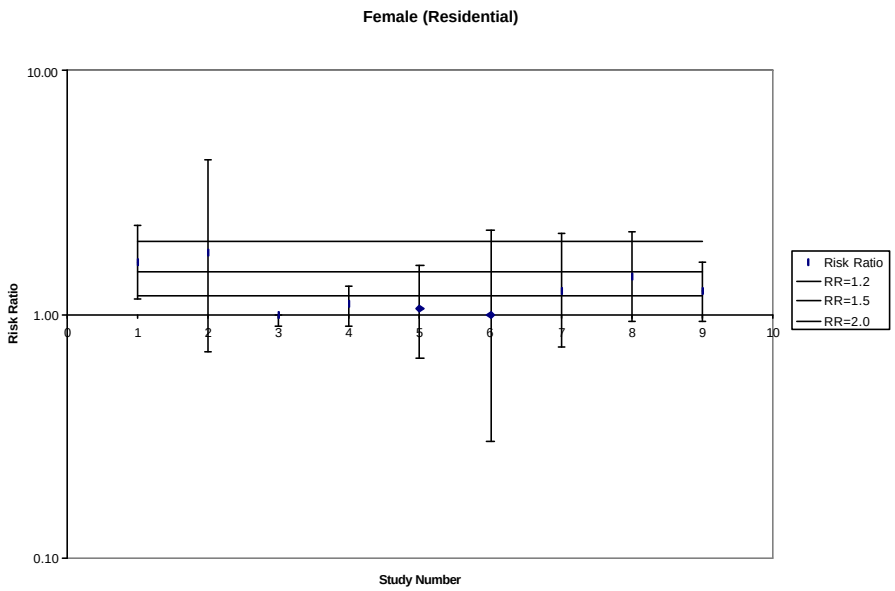

Figure 11.1.2 (Female Occupation)

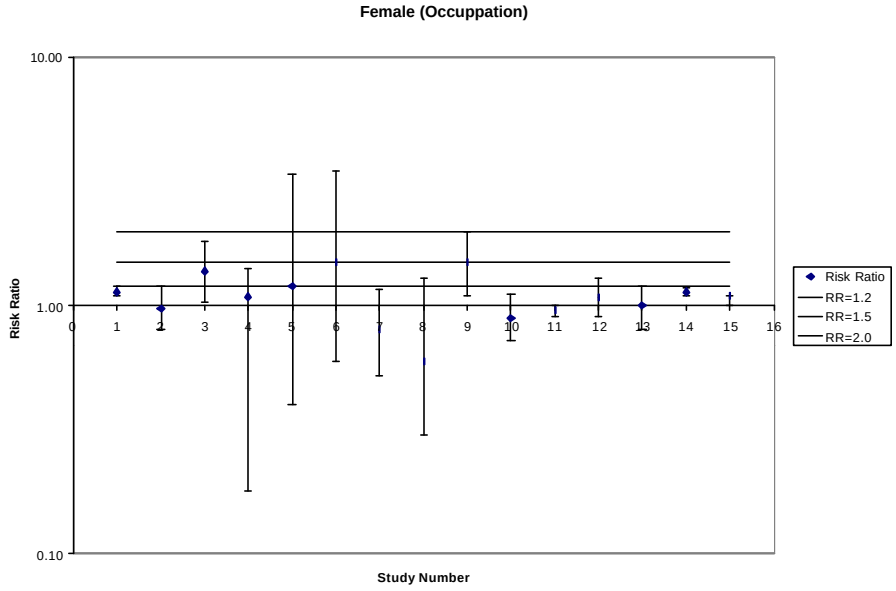

Figure 11.1.3 (Male Occupation and Residential)

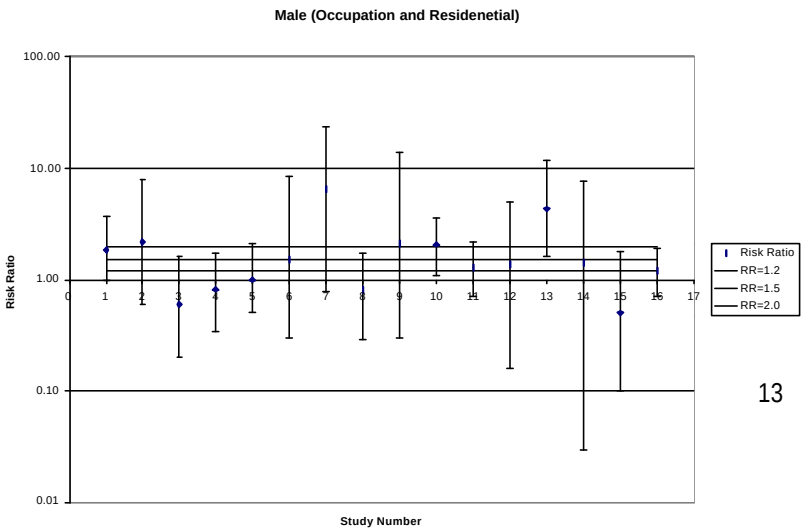

Figure 11.1.1 shows the reported relative risks and odds ratios of female breast cancer for residential power line assessment and electrical devices. These studies are listed in Table 11.1.1. Figure 11.1.2 shows the relative risks and odds ratios of female breast cancer for occupational exposures. Combining both residential and occupational exposures, 16 of the 24 relative risks are above 1.0, with an exact binomial probability of .04; 8 of the relative risks are above 1.2, with an exact binomial probability of .04. Only 2 of the studies had relative risks above 1.5; and none of the studies had relative risks above 2.0. Figure 11.1.3 shows the reported relative risks and odds ratios of male breast cancer for occupational exposures and residential exposure (one study). Eleven of the 16 relative risks are above 1.0, 10 are above 1.2, and 5 are above 1.5, respectively, with an exact binomial probability of .07, .12, and 0.07 respectively.

TABLE 11.1.1 FEMALE RESIDENTIAL AND ELECTRICAL DEVICES

STUDY NAME	STUDY NUMBER	STUDY LOCATION	STUDY TYPE	POPULATION	EXPOSURE METRIC	INDIVIDUAL ODDS RATIO, MEAN	LOWER CL	UPPER CL
(Wertheimer & Leeper, 1987)	1	USA	Mortality Case-control	<55 yrs	Wire codes	1.64	1.16	2.33
(Feychting, Rutqvist & Ahlbom, 1998a)	2	Sweden	Incidence Case-control	<50 yrs	Calc fields	1.80	0.70	4.30
(Verkasalo et al., 1996)	3	Finland	Incidence CHT	All	Calc fields > 0.01 μT	1.00	0.90	1.00
(Li et al., 1997)	4	Taiwan	Case-control		Estimated expos > 0.2 μT	1.10	0.90	1.30
(McDowall, 1986)	5	England	Mortality CHT	All	Distance < 30m	1.06	0.66	1.60
(Schreiber et al., 1993)	6	Netherlands	Mortality	All	Distance < 100m	1.00	0.30	2.20
(Vena et al., 1991)	7	NYC, US	CHT	postmeno.	Elect Blanket use (cont).	1.25	0.73	2.16
(Vena et al., 1994)	8	NYC, US	Case-control	premeno.	Elect Blanket use (cont).	1.43	0.94	2.17
(Gammon, Schoenberg & Britton, 1998)	9	US	Case-control	<10 mos use, <45 years old	Elect Bed Heater kept on	1.24	0.94	1.63

TABLE 11.1.2 FEMALE OCCUPATIONAL

STUDY NAME	STUDY NUMBER	STUDY LOCATION	STUDY TYPE	POPULATION	EXPOSURE METRIC	INDIVIDUAL ODDS RATIO, MEAN	LOWER CL	UPPER CL
(Cantor et al., 1995b)	1	US	Case-control Whites			1.14	1.10	1.20
(Cantor et al., 1995a)	2	US	Case-control Whites	Electrical workers	Title/matrix	0.97	0.80	1.20

Study Name	Study Number	Study Location	Study Type	Population	Exposure Metric	Individual Odds Ratio, Mean	Lower CL	Upper CL
(Loomis, Savitz & Ananth, 1994)	3	US	Case-control	Electrical workers	Title	1.38	1.04	1.82
(Coogan et al., 1996)	4	US	Case-control		Job Title	1.09	0.18	1.42
(Coogan & Aschengrau, 1998)	5	US	Case-control		Job Title	1.20	0.40	3.40
(Forssen, Feychting & Rutqvist, 2000)	6	Sweden	Case-control	Age<50	Matrix	1.50	0.60	3.50
(Kelsh, 1997)	7	US	Cohort	Electric utility, usual occ.	Matrix	0.80	0.52	1.17
(Vagero et al., 1985)	8	Sweden	Cohort		Job title	0.60	0.30	1.30
(Tynes et al., 1996)	9	Norway	Cohort		Title (meas)	1.50	1.10	2.00
(Fear et al., 1996)	10	England	PRR		Job title	0.89	0.72	1.12
(Guenel et al., 1993)	11	Sweden	Cohort	Occupations w potential EMF exposure	Title intermed exp	0.96	0.91	1.01
(Johansen & Olsen, 1998)	12	Denmark	Cohort	Electric util workers	Matrix	1.08	0.90	1.30
(Petralia, Chow & McLaughlin, 1998)	13	China	Cohort		Matrix	1.00	0.80	1.20
(Kliukiene, Tynes & Martinsen, 1999)	14	Norway	Cohort	Occup's with potential EMF exposure	Expert panel/ measurement	1.14	1.10	1.19
(Floderus, Stenlund & Persson, 1999)	15	Sweden	Cohort		Matrix	1.10	1.00	1.10

Table 11.1.3 Male Residential and Occupational

Study Name	Study Number.	Study Location	Study Type	Exposure	Exposure Assessment	Individual Odds Ratio, Mean
(Demers et al., 1991)	1	US, I	Case-control	Occupations w/ potent. EMF exp.	Work history, n=33 cases exposed, job title	1.85
(Loomis, 1992)	2	US, DC	Case-control	Electrical workers	Job title, n=4 cases exposed	2.20
(Rosenbaum et al., 1994)	3	US	Case-control	Occup exp. to EMF	Job title, n=6 cases exposed	0.60
(Theriault et al., 1994)	4	Canada/ France	Case-control	Electric util workers	Work history, some measurement	0.82
(Cocco, Figgs & Dosemeci, 1998)	5	US, DC	Case-control		Job matrix	1.00
(Stenlund & Floderus, 1997)	6	Sweden	Case-control	Occ. exp. to EMF	Work history, job exp matrix, some meas.	1.5
(Matanowski, Breysse & Elliott, 1991)	7	US	Cohort	Telephone workers	Current job title, some measurements	6.50
(Savitz & Loomis, 1995)	8	US	Cohort	Electric util workers	Work history, some measurement	0.8
(Feychting et al., 1998a)	9	Sweden	Case-control	Transmission line	<300 m	2.10
(Tynes et al., 1992)	10	Norway	Cohort	Electrical workers	Job title, estimate type of exposure	2.07
(Fear et al., 1996)	11	England	PRR		Job titles	1.29
(Guenel et al., 1993)	12	Denmark	Cohort	Occupations w/ potential EMF Exp, continuous	Job title	1.36
(Floderus et al., 1994)	13	Sweden	Cohort	Railway workers, 1961-69	Job title	4.30
(Tynes et al., 1994b)	14	Norway	Cohort	Hydroelectric co. workers	Work history, expos estimates	1.40
(Johansen & Olsen, 1998)	15	Denmark	Cohort	Util. workers	Job matrix	0.50
(Floderus et al., 1999)	16	Sweden	Cohort		Job matrix	1.20

TABLE 11.2.1

CHANCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Most of the results are not statistically significant.	(F1) For most of the studies, especially the male cohort studies, the number of cases were very small, resulting in low power, which explains the insignificant positive associations. All of the studies used surrogate measures to assess exposure; these measures misclassify exposure tremendously and hence may not even be predictive of exposure, thereby increasing the probability of a non-significant association.	(C1) The pattern of meta-analytic associations just above the resolution power of the studies with EMF for male and female breast cancer does not support chance as a likely explanation.
(A2) Most of the occupational cohort studies have assessed many different cancers resulting in significant "p-values," which could be due to chance.	(F2) Both meta-analyses suggest that chance is not an easy explanation of the pattern seen. For females a pooled relative risk was 1.12 (1.09-1.15) (Erren, 2001). For the male breast cancer studies, even though the disease is very rare and there was considerable random misclassification of exposure, an overall association of 1.37 (1.11-1.71) was still observed [Erren, 2001 #1534).	

TABLE 11.2.2

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The studies that assessed exposure after the occurrence of the disease may result in better recall or ascertainment of exposure for cases resulting in spurious positive results.	(F1) Observation bias is an unlikely explanation because the overall, weak positive associations of the meta-analyses for the cohort studies (where exposure was assessed prior to the occurrence of the disease) were similar to those found for the case-control studies.	(C1) If there is any bias in these studies, it is downward resulting from non-differential exposure misclassification.
(A2) Stronger positive findings were not more pronounced for those studies with more comprehensive exposure measures, suggesting that exposure misclassification is not a major problem.	(F2) Exposure misclassification bias is the major concern for all of the studies. Only crude, rudimentary estimates of exposure were used. No study directly measured a person's exposure during the critical period of time. These exposure surrogates may not even predict a person's exposure. Also, only partial exposure information was obtained—either work related or residential related, but not both. This would considerably decrease an effect. Hence, those studies with positive results would probably show a greater effect if exposure were directly measured.	

TABLE 11.2.3

CONFOUNDING		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) A weak to moderate confounder would easily "explain" the apparent weak, positive associations found for the majority of these studies.	(F1) For those positive interview studies that collected information to assess confounders, the risks were not changed after adjustment.	(C1) Important known risk factors have not been controlled for in all of these studies. However, there is no particular evidence that this would be biased to produce false-positive results.
(A2) Very few studies were able to control for important confounders such as diet, alcohol consumption, reproductive behavior and history, and other residential and occupations exposures (such as chemical exposures and x-rays) since information about the participants were from death certificates, occupation records, and census records. This could result in a bias away from the null.	(F2) For those studies that focussed on breast cancer and obtained covariate information, the control for confounding was limited because their meta-analysis results were similar to those studies where covariaties were not assessed (Erren, 2001).	(C2) Invoking unspecified confounders to explain away results is inappropriate.

TABLE 11.2.4

STRENGTH OF ASSOCIATION (*LARGE ENOUGH TO BE CAUSE NOT BIAS*?)		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) For females, no or little association has been found between breast cancer and EMF exposures. For those studies that found a positive association, the magnitude was close to one. The summary relative risk estimate from meta-analysis was 1.12 (Erren, 2001). The slight positive relationships observed for some of the studies are quite likely due to bias or some unsuspected or uncontrolled confounding variable.	(F1) All of the studies used very rudimentary estimates of residential and occupational EMF exposures. Surrogate measures of exposures may convey a risk that, due to random misclassification, is not large enough to be easily detected by epidemiological studies, and hence, are expected to convey weaker relative risks than that of a direct exposure measure.	(C1) Weak effects, if real, are of public health importance, especially those associated with common exposures and relatively common diseases such as female breast cancer. All the studies used rudimentary methods to estimate exposures, and most had a problem with power. Hence, even a modest positive association would be difficult to detect in such studies. The strength of the observed associations supports a non-causal association, but the study design issues tend to neutralize this support.
(A2) For the male breast cancer studies the summary relative risk estimate from meta-analysis was weak (1.37).	(F2) The residential studies mainly estimated high exposure as living in an area at a certain distance from transmission lines, with the cutoff range such a distance away from the transmission line that the line was not even a source of exposure for most of the participants in this group. The calculated fields generally were for buildings in this large area but not directly estimated for the location of the participant's homes. The strengths of the association were stronger from the two studies where the estimates were directly associated with the participants' residences (Wertheimer & Leeper, 1987), (Feychting et al., 1998a).	
	(F3) Those cohort studies where no male breast cancer was found had extremely low power in detecting a disease as rare as male breast cancer, thereby not contributing one way or another to the body of evidence for male breast cancer.	

TABLE 11.2.5

CONSISTENCY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The majority of the studies show a random pattern of non-significant results above and below the null, where the individual relative risk estimates are close to 1.0. This is most pronounced for the female breast cancer studies where the disease is not as rare as male breast cancer.	(F1) For the female studies, 16 out of 24 studies revealed a relative risk of above 1.0.	(C1) The evidence is modestly consistent.
	(F2) Also, for the male breast cancer, across all 16 studies, there were 11 with relative risks above 1.0 ($p = 0.07$).	

TABLE 11.2.6

HOMOGENEITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is a lack of homogeneity for a positive association across studies supporting the possibility of a chance occurrence.	(F1) The extreme heterogeneity in population definition across studies and the crude and widely different methods used to assess exposure for all studies make it difficult to evaluate homogeneity.	(C1) The lack of homogeneity across studies does not necessarily decrease the likelihood of a causal relationship. This may be due to the difference in the definition of study populations and exposure assessment across studies.
(A2) Some studies found a slight positive association for some population subgroups. However, these particular subgroups were not the same from study to study. The lack of homogeneity in various subgroups suggest that the positive associations found are more likely to represent chance fluctuations in the data than true increased risk.	(F2) Homogeneity was observed for those subgroups adequately defined and where an increased risk of breast cancer is expected. Not all studies looked at similar subgroups and most studies were not able to evaluate subgroups due to a small number of cases.	(C2) The pattern for the female breast cancer results is heterogeneous, making it difficult to either support or refute its causal association with EMF.
(A3) For the male breast cancer studies no breast cancers were found for the seven cohort studies (see Erren, 2001) supporting the notion that the weak meta-analysis risk estimate is probably due to chance.		

TABLE 11.2.7

DOSE RESPONSE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) No consistent gradient is found, even in the occupational studies, where higher exposures are expected relative to residential environments and in the electric bed heater studies where these devices are expected to emit strong fields and occur at night, which is the time most likely to influence the natural circadian rhythm of melatonin production (one of the main biological hypotheses for breast cancer). The likelihood of a causal relation is strengthened if a dose-response effect is found.	(F1) A dose-response relationship can frequently be masked by an inability to measure exposure sufficiently to distinguish between risks associated with different levels. A dose response cannot be adequately assessed for the breast cancer studies. Most of the studies only included one level of EMF exposure, and those that had data on two or more levels used surrogate estimates of exposure associated with a high level of misclassification into high to low exposure groups. These studies used different exposure groupings to assess dose response. The electric bed heater studies did not assess a gradient in exposure but rather a gradient in the duration of use, and one study did not differentiate among the types of bed heaters. Also, it may be that electric bed heaters do not emit fields as strong as once thought (Lee et al., 2000).	(C1) The absence of a dose-response gradient does not mean that a cause-effect relationship does not exist. Moreover, it is not unusual for biologic factors to demonstrate a threshold phenomenon, where no effect is present until a certain level of the exposure is reached.
	(F2) Of the 22 studies which present some kind of very crude estimate of an EMF dose, 8 suggest that there might be a dose-response relationship (Vena et al., 1991), (Vena et al., 1994), (Demers et al., 1991), (Tynes et al., 1996), (Coogan et al., 1996), (Li et al., 1997), (Feychting et al., 1998a), (Kliukiene et al., 1999), (Forssen et al., 2000). One of these studies found the strongest relationship for men exposed before age 30 and where > 30 years elapsed before diagnosis (Demers et al., 1991).	(C2) The studies that categorized different levels of exposure used crude estimates (i.e., the categories defined as "high" to "low" groups may not actually reflect low to high exposures). The misclassification of exposure along with the rarity of the disease, especially for males, decreases the ability of the studies to detect a dose response. Hence, a lack of a dose-response gradient does not support a non-causal association.

TABLE 11.2.8

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Everyone is exposed to electricity so we should have seen an epidemic of breast cancer as the use of electricity increased. No clear epidemic has been demonstrated.	(F1) There has been a slight increase in the age-adjusted incidence of, at least female, breast cancer over the last twenty years. Also, there is an increased rate in industrialized regions compared to non-industrialized regions. This implies that risk increased with increase of electricity use.	(C1) It is possible that, over time, EMF exposure may be more variable as environmental sources increase via industrialization. However, an increase in industrialization or urbanization also may be associated with an increase in other important breast cancer potential risk factors. Hence, visibility does not influence the likelihood of causation one way or the other.
(A2) A more pronounced risk was not observed for the most heavily exposed groups.	(F2) The assessment of a heavily exposed group was based on very crude measures where this group may not have high exposures. Furthermore, very few studies were able to evaluate the effect for heavily exposed groups compared to those with little or no exposures.	(C2) The consistency of a slightly stronger association with more vulnerable subgroups suggests a slight coherence of the results. However, this does not necessarily support a causal association because these subgroups were crudely defined, and only a small number of studies assessed these subgroups.
	(F3) Of the few studies that assessed more homogenous subgroups, the effect was more pronounced for those groups assumed to be susceptible to breast cancer. Overall, the effect was somewhat higher for younger or pre-menopausal women (Wertheimer & Leeper, 1987), (Forssen et al., 2000), (Coogan et al., 1996), (Coogan & Aschengrau, 1998), (Gammon et al., 1998) especially for those with estrogen positive breast cancer (Feychting et al., 1998a), (Forssen et al., 2000).	
	(F4) The summary, weak positive relative risk estimates from the meta-analyses were similar regardless of study design and country (US vs. other) of the study population.	

TABLE 11.2.9

EXPERIMENTAL EVIDENCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Overall, the animal bioassays have been inconsistent with most studies not supporting an association of exposure with mammary tumors.	(F1) Several studies support an association with mammary tumors, and two studies showed a dose-response relationship (Loscher et al., 1994), (Mevissen et al., 1996a).	(C1) Some of the promotional animal studies have been positive with two showing a dose response, thereby supporting a causal hypothesis.

TABLE 11.2.10

PLAUSIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) A specific biologic mechanism involving the suppression of the nighttime hormone, melatonin, has been proposed to increase cancer risk. The animal evidence is not consistent with this hypothesis, especially the large animal studies, which are consistently negative. Unidentified, critical parameters result in the false positives observed for some of the few small animal studies.	(F1) EMF exposures do affect melatonin as observed in some small animal studies; however, the lack of consistency is the result of not yet defined critical parameters that mediate the response. For these studies there is misclassification and bias for most of the existing data. There are fewer studies with large animals than with small animals, and these studies mainly assess circulating melatonin. Also, among the animal studies there are a number of different endpoints assessed as to the synthesis, secretion, and metabolism of melatonin, thereby increasing the likelihood of observing inconsistency across these studies.	(C1) There is a specific biological rationale associated with EMF exposure and breast cancer risk, which has, to some extent, been supported by animal studies.
(A2) Even though a melatonin-cancer association has been observed, an EMF-melatonin link has not been established. For the positive animal studies, only small reductions of melatonin after EMF exposure have been observed. Given the large variation of melatonin in humans, it is unclear how a small reduction in melatonin, as observed in the animal studies, could result in an adverse health effect.	(F2) Other experimental and laboratory studies, such as the *in vivo* rodent experiments (where deprivation of pineal function increases tumor incidences) and the *in vitro* MCF-7 cell line studies (showing the anti-proliferative nature of melatonin) support the small animal findings.	
	(F3) There are well-established risk factors with unknown mechanisms.	

TABLE 11.2.11

ANALOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 11.2.12

TEMPORALITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 11.2.13

SPECIFICITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 11.2.14

OTHER DISEASE ASSOCIATIONS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
See "Generic Issues" chapter.		

TABLE 11.2.15

SUMMARY TABLE FOR BREAST CANCER			
HOW LIKELY IS THIS ATTRIBUTE OF THE EVIDENCE UNDER:			
ATTRIBUTE OF THE EVIDENCE	**"NO-EFFECT" HYPOTHESIS**	**CAUSAL HYPOTHESIS**	**HOW MUCH AND IN WHAT DIRECTION DOES THIS ATTRIBUTE CHANGE CERTAINTY?**
Chance is unlikely.	Possible	Less possible	Some increase
Upward bias not supported.	Possible	Possible	No impact
Confounding possible but not supported.	More possible	Possible	No impact or slight decrease
Combined chance, bias, confounding.	More possible	Possible	Slight decrease
Strength of association: (1) does not exceed possible bias or confounding.	More possible	Possible	No impact
Strength of association: (2) a weak positive pattern for female breast cancer but with considerable heterogeneity; a weak positive pattern for male breast cancer slightly supported.	Female: possible Male: possible	Female: possible Male: more possible	No impact or slight increase
Consistency and homogeneity across studies is modest.	More possible	Possible	No impact or slight decrease
Dose response is difficult to evaluate.	Possible	Possible	No impact
Coherent with national and temporal trends.	Possible	Possible	No impact
Experimental evidence slightly supported.	Possible	More possible	No impact or slight increase
Plausible mechanistic melatonin explanation has some support.	Possible	More possible	No impact or slight increase
Lack of analogous agent.	Possible	Possible	No impact
Temporality: exposure precedes disease.	Possible	Possible	No impact
No specificity, other disease associations.	Possible	Possible	No impact

11.3 Posterior (Updated) Degree of Certainty and IARC Classification

11.3.1 Statements of Individual Reviewers

Reviewer 1 (DelPizzo)

Female Breast Cancer

The epidemiological studies are rather consistent in indicating a relative risk of 1.1. Overall, there are 27 risk estimates greater than 1, out of 40 studies. The p-value for such a pattern is < 0.01, arguing that that chance is not a plausible explanation. In addition, there is some directly pertinent animal evidence in support of the hypothesis, and, as in the cases of other endpoints, no convincing alternative explanation for the association. Reviewer 1 is "close to the dividing line between believing and not believing." He would use certainty values between 35 and 80 with a median value of 49.

IARC classification: Because of the limited quality of human studies and the lack of published replication of animal studies, Reviewer 1 believes that the most prudent classification under these guidelines is inadequate evidence.

Male Breast Cancer

There are only a few human studies, with some suggesting a considerably stronger association than others. This is boosted somewhat by the high degree of certainty attributed to other associations, particularly female breast cancer, but overall the evidence falls short of reaching the 51 confidence level. Reviewer 1's evaluation is "close to the dividing line between believing and not believing." For decision analysis purposes, Reviewer 1 would use values between 30 and 75 with a median of 45.

IARC Classification: Inadequate evidence.

Reviewer 2 (Neutra)

Female Breast Cancer

Degree of Certainty: While 16 of the 24 studies reviewed had odds ratios above 1.0 (which is an improbable distribution), Erren's (Erren, 2001) meta-analytic summary OR was 1.1 (1.09-1.15). Nonetheless, there was substantial heterogeneity among the studies, most of which had very crude indices of exposure. The melatonin hypothesis which motivated these studies requires that the effect of EMFs on lowering melatonin in humans be clearly demonstrated and that the in vivo oncostatic effect of modest increases in melatonin be clearly demonstrated. Neither of these conditions has been met definitively. The unreplicated Loscher experiments did not affect this reviewer. For all the reasons given in the discussions above, this pattern of evidence increased Reviewer 2's confidence about female breast cancer only slightly above the prior. With an association close to the resolution power of the studies, this reviewer's degree of certainty would best be expressed as being on the low side of "prone not to believe" with a median of 11 and a range from 2 to 45.

IARC Classification: The lack of clear animal pathology or mechanistic support and the weakness of the epidemiological support to date would make this body of evidence "inadequate" to implicate EMFs as carcinogens and falls into Group 3.

Male Breast Cancer

Degree of Certainty: The pattern of associations for male breast cancer in the studies reviewed by Erren (Erren, 2001) shows 11 of 16 with odds ratios above 1.0 (p = 0.07), while Erren's meta-analytic summary was 1.4 (1.1-1.7). The higher odds ratios reported in the early 1990s have not persisted in the later studies. The other streams of evidence have been discussed above and have similar weights as with female breast cancer. The overall pattern of evidence has increased this reviewer's degree of certainty upward from what it was originally.

With the prior degree of certainty for a just-detectable effect, this reviewer's posterior degree of certainty would best be describes as "prone not to believe" with a median of 39 and a range from 2 to 60.

IARC Classification: The lack of definitive animal pathology and mechanistic explanation and the less than conclusive epidemiology would leave this body of evidence as "inadequate" to implicate EMFs as a carcinogen and falls into Group 3.

Reviewer 3 (Lee)

Female Breast Cancer

Degree of Certainty: The human evidence of female breast cancer is based on occupational and residential studies, both of which used extremely crude methods to estimate exposures and had low power to detect weak associations. The relative likelihood of a consistently weak positive association across studies does not influence Reviewer 3's prior for a relative risk around 1.2. Mainly, this reviewer's posterior prior is slightly increased over her prior by the support of the animal

evidence and by the positive EMF association with childhood leukemia. Hence, the posterior degree of certainty for purposes of the policy analysis falls within the "prone not to believe" category with a median of 15 and a range of 5 to 35.

*IARC Classification***:** The human evidence is inadequate where most studies were not primarily designed to test an EMF-related hypothesis, most lack power, and most are susceptible to biases and confounding due to the crude exposure estimates. The overall relative risks are weak where chance cannot be ruled out as an explanation. On the other hand, the animal evidence supports a clear biological model with some inconsistencies. Furthermore, there is evidence that the proposed mechanism operates in humans. Given this, along with support from the childhood leukemia findings, the evidence is in the upper end of the Group 3 classification, "inadequate."

Male Breast Cancer

Degree of Certainty: Like the female breast cancer evidence, the human evidence of male breast cancer is based on both occupational and residential studies that used extremely crude methods to estimate exposures and had low power to detect weak associations. Reviewer 3's posterior is slightly increased above her prior by the consistently weak positive association across studies, by the support of the animal evidence, and by the positive EMF association with childhood leukemia. Hence, the posterior degree of certainty for purposes of the policy analysis falls within the "Prone not to Believe" category with a median of 20 and a range of 10 to 45.

IARC Classification: This is similar to that of female breast cancer. The human evidence is inadequate where most studies were not designed to test an EMF-related hypothesis, most lack power, and most are susceptible to biases and confounding due to the crude exposure estimates. The overall relative risks are weak, where chance cannot be ruled out as an explanation. On the other hand, the animal evidence while suggestive (Loscher) has some inconsistencies. There is some evidence that the proposed mechanism operates in humans. Nonetheless the evidence is at the upper end of the Group 3 classification, "inadequate."

11.3.1 SUMMARY OF THE THREE REVIEWERS' CLASSIFICATIONS

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFS) INCREASE DISEASE RISK TO SOME DEGREE
Breast Cancer, Female				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	
	2	3	Prone not to believe	
	3	3	Prone not to believe	
Breast Cancer, Male				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	
	2	3	Prone not to believe	
	3	3	Prone not to believe	

11.4 Questions Relevant to Dose Response and Policy

Table 11.4.1

HOW CONFIDENT ARE THE REVIEWERS THAT SPECIFIC EXPOSURE METRIC OR ASPECT OTHER THAN 60 HZ TWA MAGNETIC FIELD IS ASSOCIATED WITH THIS DISEASE?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	

Table 11.4.2

EVIDENCE FOR THRESHOLD OR PLATEAU	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	

Table 11.4.3

EVIDENCE FOR BIOLOGICAL WINDOWS OF VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	

Table 11.4.4

CONSISTENT INDUCTION PERIOD OR REQUIRED DURATION OF EXPOSURE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	

TABLE 11.4.5

EMFs COMPARED TO OTHER RISK FACTORS FOR THIS DISEASE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) The few known risk factors for breast cancer show weak to moderate associations, generally larger than those found for the EMF-breast cancer studies. However, the studies evaluating these other risk factors used better exposure-measurement protocols than those assessing the EMF-breast cancer association. (C2) The common prevalence of both the exposure and at least female breast cancer could result in a considerable public health burden even if the true effect is weak. However, due to the poor quality of exposure data, the low power, and for some studies the low participation response rate of the breast cancer, it is difficult to compare the strengths found for the breast cancer studies with the strengths of known risk factors.	No impact.

TABLE 11.4.6

RELATIVE RISK COMPARED TO THAT WHICH WOULD GENERATE 1/1000 OR 1/100,000 THEORETICAL LIFETIME RISK	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) A relative risk of 1.12 for female breast cancer applied to moderate baseline rate of female breast cancer over a 40-year period would exceed a 1/1000 lifetime risk. (C2) A relative risk of 1.37 applied to the very low baseline rate of male breast cancer over a 40-year period would not exceed a lifetime risk of 1/1000 but may exceed a 1/100,000 lifetime risk.	(I1) The risk could be of regulatory concern if real.

TABLE 11.4.7

EVIDENCE FOR RACIAL OR CLASS DIFFERENCES IN EXPOSURE OR VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base	

TABLE 11.4.8

ROOM FOR IMPROVEMENT IN QUALITY OR SIZE IN BEST EXISTING STUDIES	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) There is room for improvement in all studies in one way or another. All studies had one or more of several major problems in design, making it difficult to assess if the overall weak positive relationship observed could be due to chance or could reflect a causal association.	

TABLE 11.4.9

NEW STUDIES IN PIPELINE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) There are 5 female breast cancer studies currently in progress (Davis; London; Fechting; Demers and Weis; and Long Island Breast Cancer study). These studies have better exposure assessment protocols and are collecting important risk factors to adequately assess confounding. There are no male breast cancer studies currently in progress.	(I1) If all 5 studies showed an association this would drive policy; otherwise the question would remain open.

TABLE 11.4.10

HOW LIKELY IS IT THAT FURTHER STUDIES COULD RESOLVE CONTROVERSIES?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Somewhat likely for female breast cancer, depending on the design of future studies. Studies need large number of women in EMF-related jobs defined specifically for women, not men, for occupational studies and residential studies that estimate personal exposures. Also, the new studies should take into account shift work or light at night, include residential and occupational exposures, define exposures that may capture a dose-response, and evaluate timing, assess potential confounders adequately, and assess menopausal status as well as disease estrogen-receptor status.	(I1) Studies are worth pursuing, especially for female breast cancer.

11.5 Conclusions on Scientifically Relevant Issues

11.5.1 Dose-Response Issues

The associations reported for residential power lines, electrical bed heaters, and occupational exposures (utility workers with assumed high EMF levels) are all close to the resolution power of the studies. If there is any effect, it does not seem to increase monotonically with dose, although, due to the crude assessment of exposure, the evidentiary base is insufficient for identifying either thresholds or plateaus of effect. Even though there is a plausible biological model with some support from animal studies, it may be difficult to capture even a dose response in bioassay studies that are designed with the assumption that high doses will produce an obvious effect even in a few hundred animals. The component of the electric magnetic field that may be a biologically active agent has not be adequately explored because all studies only assessed surrogate estimates for exposure.

11.5.2 Research Policy

No studies are currently in the pipeline for male breast cancer. There are five epidemiological female breast cancers in the pipeline. If all five studies result in positive findings, this would change the overall policy assessment because these studies are using better exposure assessment and are better able to address confounding compared to the currently published studies. A few large job-matrix studies designed for female occupations and using various summary exposure metrics would allow one to reanalyze the current large case-control studies to determine what aspects of the EMF mixture might better explain the associations seen with breast cancer and other diseases. From a policy and logistic point of view, female breast cancer studies are a high priority, due to the prevalence of the disease. The evidence for an association with the surrogate estimates of EMF is compatible with a 1.12-fold relative risk for females, which if true, would be of regulatory concern for long-term environmental and occupational exposures, especially for females.